

**National Institutes of Health
National Institute of Biomedical Imaging and Bioengineering**

**Optical Imaging Program
Progress Review**

**Bethesda, Maryland
June 13, 2007**

**PROGRESS REVIEW GROUP
REPORT**

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Overview and Charge to the Progress Review Group

The Optical Imaging Program Progress Review Group (PRG) was convened by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) on June 13, 2007 as part of an ongoing process of program assessment. The PRG process is comprised of three phases:

- Phase 1 will assess the state of the portfolio and the science with input from research, technology development, and clinical communities and will result in a report to serve as a baseline from which to measure progress.
- Phase 2 will plan for and implement strategies to achieve scientific advances and address gaps and needs based on the state of the science. Cost, feasibility, available infrastructure, potential impact, and opportunities for partnerships, among other details, will be considered.
- Phase 3 will report on progress made in advancing the state of the science typically 5 years after the baseline report. This report will consider initiatives implemented, the grant portfolio, scientific publications, and research accomplishments in novel or emerging areas. On the basis of this report, course corrections will be made as needed.

Each review cycle is expected to take about 5 to 6 years and is intended to assess the state of the science and establish milestones from which future progress will be measured. Thus, the process of program progress review will both chart future courses and provide accountability.

The meeting of the Optical Imaging Program PRG marks the first time NIBIB has convened a group to assess a strategic area within its scientific portfolio. Specifically, the PRG was charged with assessing the state of the science, assessing the NIBIB grant portfolio in the context of the overall National Institutes of Health (NIH) portfolio, and identifying research gaps, resource needs, and areas of interest for future research.

In welcoming PRG participants, Dr. Roderic Pettigrew, Director, NIBIB, emphasized the importance of gathering diverse viewpoints and pointed out that the goal of this meeting was not necessarily to reach consensus. He cited James Surowiecki's *The Wisdom of*

Crowds and remarks by Nobel Laureate Charles Townes, inventor of the laser and speaker at the NIBIB Fifth Anniversary Symposium, as further support for bringing together experts from various fields. He also broadened the scope of discussion beyond imaging to optical diagnostics and technologies and encouraged PRG members to share their opinions in those areas.

Following presentations by Dr. Belinda Seto, Deputy Director of NIBIB, Dr. William Heetderks, Director of Extramural Science Programs, and Dr. Yantian Zhang, Program Director in the Division of Applied Science and Technology, PRG participants engaged in an open discussion.

This PRG report, which represents the product of the first phase of the PRG process for the Optical Imaging Program, provides an overview of the current portfolio and state of the science, outlines top research priorities and resources needed to address a given research area, and serves as a benchmark from which progress can be assessed. A key element of this report is a list of opportunities that will help advance future research. The PRG included clinicians, physicists, chemists, engineers, and experts in optical science (see Attachment 1 for the list of PRG members and NIBIB meeting participants). Each PRG member was given an opportunity to review, comment on, and approve the final PRG report.

The PRG team will summarize the findings of this report and present them to the NIBIB National Advisory Council for discussion and suggestions. Following review by the NIBIB Director, the PRG Report will be published and widely disseminated. The electronic version of the PRG Report will be posted on the NIBIB Web site to facilitate public access and comment.

The NIBIB Mission

William Heetderks, M.D., Ph.D., Director, Extramural Science Programs, NIBIB

On December 29, 2000, President Clinton signed into law an act passed by Congress to establish the NIBIB. The legislation mandated that NIBIB:

- Research and develop **new** biomedical imaging and bioengineering techniques and devices.
- Enhance **existing** imaging and bioengineering modalities.
- Support **related research** in the physical and mathematical sciences.
- Encourage research and development in **multidisciplinary** areas.
- Support studies to assess the **effectiveness and outcomes** of new biologics, materials, processes, devices, and procedures.
- Develop technologies for **early disease detection and assessment** of health status.
- Develop advanced imaging and engineering techniques for conducting **biomedical research at multiple scales**.

The leadership at NIBIB underwent a lengthy strategic planning process to distill the legislation into a mission to improve human health by leading the development and accelerating the application of biomedical technologies and to integrate the physical and life sciences to advance basic research and medical care.

The NIBIB strategic plan established several goals to implement this mission.

- A strong extramural research community focused on discovery, development, and application of science and technology to improve health. This means maintaining a payline and a core of grants in important research areas while supporting broad programmatic areas that should be encouraged further.
- Targeted research programs in areas of special opportunity or need that take advantage of novel technological advances and scientific discoveries.
- Accelerated translation of promising technologies to improve human health.
- Reduced health disparities through new and affordable medical technologies.
- An intramural research program with interdisciplinary emphasis.

From its beginning, NIBIB enjoyed a sharp yearly increase in funding until FY2004 and then the budget flattened. The NIBIB budget is about \$300 million, about 1% of the NIH budget. The vast majority of funding supports extramural research through R01 and R21 mechanisms, and the majority of these grants are awarded to institutions of higher education, medical and engineering schools. Grants support includes a wide range of programs, including bioengineering, platform technologies, magnetic resonance imaging, biomaterials, nuclear medicine, optical imaging, telemedicine, x-ray, and many others. The NIBIB budget also includes a small number of large awards, as well as funds for NIH Roadmap initiatives. The Institute plans for multiple budget scenarios such that it can capitalize on ideas when opportunities present themselves.

In response to questions about the position of NIBIB relative to other NIH Institutes and Centers (ICs), Dr. Pettigrew noted that at nearly \$300 million in research and training budget authority, NIBIB is much smaller compared with established ICs such as the National Cancer Institute (NCI; \$4.7 billion in FY2007), the National Institute of Allergy and Infectious Diseases (\$4.4 billion), or the National Heart, Lung and Blood Institute (NHLBI; \$2.9 billion) but is larger than the Fogarty International Center (\$67 million) and most of the NIH Centers. Several ICs support technology development; for example, the NCI has a strong imaging program comparable in size to that of NIBIB. The key difference is that basic research for technology development is at the heart of the NIBIB mission. NIBIB works closely with the National Center for Research Resources (NCRR) in its support of P41 resource center grants. However, the NCRR supports a broader range of research resources and their development, and is more than three times larger than NIBIB with more than \$1 billion in research and development budget authority.

Overview of the Current Optical Imaging Program

Yantian Zhang, Program Director, Division of Applied Science and Technology, NIBIB

The NIBIB Optical Imaging Program supports research on the development and applications of optical imaging. The Optical Imaging Program covers research and application of imaging that resides in and around the visible region of the electromagnetic spectrum. Other techniques, such as positron emission tomography, magnetic resonance imaging, and x-ray imaging also use photons at different energy levels for imaging purposes, but these techniques are organized in other NIBIB extramural imaging programs. Even with these exclusions, however, the Optical Imaging Program is very broad and encompasses a wide range of image signal sources, signal detection, and imaging physics.

Moreover, the range of applications for optical imaging is very diverse and covers almost the entire landscape of scientific disciplines. The Hubble telescope, which has brought us pictures of distant stars and galaxies, is a well-known example of optical imaging application in physics. At the other end of the spatial scale, in chemistry, optical imaging and other means of optical detection are used in nanophotonics, in molecular spectroscopy, in liquid and gas chromatography, and in measurement of zeta potential, etc. In biology, microscopes are the most commonly used scientific instruments such as conventional and more recent confocal, multiphoton microscopy, and other non-linear microscopies that have extended our vision into ultra-small world of cellular machinery. Microscopy is also very widely used in medicine, for example, in examining histopathology in disease diagnosis or clinical assessment. Overall, it is evident that technology development and technology applications are closely coupled together in a development-applications circle, i.e., new applications arise from technological advances, new applications in turn drive further technology developments.

Specific examples of optical imaging research supported by the NIBIB includes:

- Optical coherence tomography (OCT),¹ is an emerging imaging modality which can generate high-resolution, cross-sectional images of microstructure in biological systems. Following a long path to commercialization, OCT is now widely used in ophthalmology (over 6,000 units of the Stratus OCT made by Carl Zeiss Meditech have been sold to date) to look at the retina *in vivo* and diagnose diseases such as diabetic retinopathy, glaucoma, and macular degeneration. Recent advances in light sources, image acquisition strategies, and in computational techniques have pushed OCT even further, dramatically improving resolution and thus allowing the acquisition of thousands of images per second at high resolution.
- Confocal and two-photon microscopy (TPM),² have allowed biomedical research to move beyond prepared slides of cells or tissue to in-depth imaging *in vivo*. Confocal microscopy images only in the focal plane by rejecting contaminating out-of-focus

¹ Huang D, Swanson EA, Lin CP, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, et al. Optical coherence tomography. *Science* 1991;254:1178–81.

² Denk W and Svoboda K. Photon upmanship: Why multiphoton imaging is more than a gimmick. *Neuron* 1997;18:351–7.

signals through the use of a small pinhole. It is somewhat limited in light collection and excites large sample volumes. Like confocal imaging, multiphoton microscopy, a technique that non-linearly excites a small focal volume, is able to produce high-resolution 3D optical images but with the additional benefit of reduced photobleaching and photodamage. Other new forms of super-resolution microscopies are recently emerging such as PALM (PhotoActivatable Light Microscopy), STED (STimulated Emission Depletion), and SI (Structured Illumination) as are label free microscopies such as CARS (Coherent Anti-Stokes Raman Scattering).

- Molecular optical imaging techniques.³ These techniques have arisen as a result of problem-oriented, interdisciplinary research in which technological solutions were developed to address biological problems. Researchers can now investigate biological questions at cellular and molecular levels. Molecular optical imaging techniques have been employed in a wide range of applications, including tumor detection, imaging of apoptosis using near-infrared fluorescence probes, imaging of viral proteases, *in vivo* bioluminescence imaging, serial imaging of tumor response to therapy, and neural precursor cell tracking.

A PubMed search reveals that the number of publications focused on various optical imaging techniques has steadily increased since 2000. Optical imaging techniques are also the subject of many ongoing clinical trials, as a search on the Clinicaltrial.gov website indicates. OCT is now used in ophthalmology practices. Thus, optical imaging is not just a research interest; it is clinically relevant.

The Optical Imaging Program is a modestly sized program. Approximately \$16 million is committed each year and supports about 80 grants across a wide range of topics, including optical microscopy, OCT, fluorescence, and bioluminescence imaging, confocal and multiphoton microscopy, diffuse optical tomography, nonlinear optics, devices, etc. The underlying physical principles of these imaging technologies differ from each other. Some projects are high-risk, high-impact research project grants funded as R01s and R21s. The program portfolio also includes several other grant mechanisms, including two P41 grants and a number of Small Business Innovation Research grants.

Several examples of projects supported by the Optical Imaging Program are:

- *In vivo* intravascular OCT imaging of vulnerable plaques (Mark Brezinski, Brigham and Women's Hospital, Harvard Medical School). In this project, OCT is used to detect plaques and measure the fibrous cap thickness which is one of the indicators for plaque rupture vulnerability. The technology is relatively mature for clinical translation and the clinical impact is potentially large. Traditional microvessel staining does not provide information about the composition of the plaque caps and how likely a plaque is to rupture. Polarization-sensitive OCT, which looks at the properties of collagen, provides information about the extent and organization of collagen in the fibrous caps and thus may

³ Shah K and Weisslander R. Molecular optical imaging: Applications leading to the development of modern-day therapeutics. *NeuroRx* 2005;2:215–25.

serve as an indicator whether a plaque is predisposed to progression to unstable angina and myocardial infarction.

- Optical spectroscopy for minimally invasive pancreatic cancer risk-stratification (Vadim Beckman, Northwestern University). Dr. Beckman's goal in this project is to demonstrate the feasibility of a minimally invasive optical technique to diagnose pancreatic cancer. He used four-dimensional elastic light scattering spectroscopy and low coherence enhanced backscattering spectroscopy to interrogate biopsies taken from the lining of the nearby upper small intestine. In the small pilot study involving 51 individuals, both techniques demonstrated high levels of sensitivity (95%) and specificity (91%) in identifying pancreatic cancer. The study results are being reported in a recent issue Clinical Cancer Research.
- *In vivo* optical detection of dysplasia in Barrett's Esophagus (Lev Perelman, Harvard Medical School). Random biopsy in Barrett's Esophagus patients is prone to sampling error and often results in increased cost and risk of surveillance for detection of carcinoma. Dr. Perelman's research aims to develop a diagnostic screening tool to enable a gastroenterologist to rapidly survey the region of Barrett's esophagus, and to identify in real time the high probability regions of dysplasia and carcinoma. The instrument is based on the technique of light scattering spectroscopy. The research has the potential of reducing the number of biopsies and the associated sampling errors, reducing patient discomfort, and more importantly, making the diagnosis more consistent and based on quantitative criteria.
- Laser ablation followed by Two Photon Microscopy (D. Kleinfeld, University of California, San Diego). Laser ablation offers tremendous advantage in sectioning tissues, particularly by reducing artifacts generated by traditional sectioning techniques. Combining laser ablation with TPM allows one to examine unperturbed cellular constituents in tissue sections. This method has been used to manipulate microvessels and thus generate a model of microstroke in rat brain. The laser process introduces clotting, and TPM measures blood flow. Laser ablation/TPM has thus helped researchers perturb the vascular system at the microscopic scale and study the vascular response to clotting. This technology will ultimately lead to a better understanding of the pathology of, and physiologic response to, stroke.
- Fluorescence recovery after photobleaching of brain cortex (A. Verkman, University of California, San Francisco). Researchers on this project use novel optical imaging techniques to examine biological processes, such as DNA diffusion in the cytoplasm, diffusion in the mitochondrial matrix, and diffusion in the extracellular space in the brain and in tumors. The goal of the research is to construct an accurate picture of the cell interior based on measurements of solute mobility and interactions.
- The use of multiphoton microscopy to image beta-amyloid senile plaques in an animal model (B. Bacskaï, Massachusetts General Hospital, Boston, MA). This

imaging method is used to monitor plaque size, dystrophy, and distorted neurites over time and thus has potential application in drug trials assessing the effects of treatments for Alzheimer's disease.

- Quantum dot (QDot) development and application (J. Frangioni, Beth Israel Deaconess Medical Center, Boston, MA). QDots have high photostability and controllable emission wavelengths. This research has focused on the development of near-infrared QDots with improved optical performance *in vivo*. Using large animal model systems the size of humans, QDots have been optimized for sentinel lymph node mapping and other clinical applications in image-guided surgery.
- QDot single-cell imaging (S. Weiss, University of California, Los Angeles). Quantum dots have been used to follow cellular movements in zebrafish embryos, which are labeled with QDots when they are in the single cell stage, and to monitor how QDots contained in vesicles enter the cell and the nucleus. QDot single-cell imaging could potentially be useful in the development of more targeted therapies for a variety of human diseases.
- QDot surface modifications in animal imaging (B. Ballou and A. Waggoner, Carnegie Mellon University). By modifying QDots surface with polyethylene glycol coating the half-life of QDots in the blood can be significantly improved by avoiding trapping in the liver too quickly.
- Optical molecular imaging (G. Wang, University of Iowa, Iowa City, IA). A problem facing bioluminescence imaging to track cellular and molecular events is the tissue scattering of light by tissue, which results in images with poor resolution. To circumvent this limit, researchers have used a photon transport model that describes the composite photon propagation in tissue and air. Images are constructed using projection images from multiple angles.
- Fluorescence Molecular Imaging (V. Nitzachristos, Massachusetts General Hospital). This imaging technique has been used to examine proteolytic activity during lipopolysaccharide-induced pulmonary inflammation. The results demonstrated the feasibility of Fluorescence Molecular Imaging in imaging specific bioactivity using activatable fluorescent probes.

In addition to that from NIBIB, optical imaging enjoys a wide range of research support across the NIH, particularly from the NCI, the NHLBI, the National Institute of General Medical Sciences (NIGMS), and the NCRR. NIGMS supports microscopy with a focus on applications at the microscopic scale, whereas NIBIB supports microscopy that will have some macroscopic applications *in vivo* at the level of tissue and higher. NIH Roadmap grants are another means of supporting these applications. In addition, NCI's Cancer Imaging Program has provided considerable support for optical imaging research. One such example is the NCI Network for Translational Research in Optical Imaging (NTROI) Program, a multi-institution network focused on coordinating research and industry to speed up the translation process.

Although it is difficult to predict what the future holds, NIBIB remains dedicated to its mission of bridging the life and physical sciences, supporting optical imaging research and application, encouraging exploration of high risk but potentially high impact research, and supporting basic research. NIBIB, and NIH overall, are particularly interested in opportunities for translational research.

PRG Discussion Highlights

Potential research areas

No gaps were identified in the Optical Imaging Program research portfolio, but several opportunities merit further exploration.

A significant portion of the discussion was devoted to optical contrast agent development. NIBIB is leading a Roadmap initiative focused on high-specificity, high-sensitivity imaging probes. This project will move out of the Roadmap incubator space into NIBIB in 2009. Dr. Seto pointed out that NIBIB has an opportunity to reconstitute the makeup of that initiative to ensure that the institute capitalizes on scientific opportunities. PRG members discussed roadblocks to developing optical contrast agents commercially (see Barriers to Translation, below) and noted the dependence of optical imaging on the strength of fluorophores themselves. They also commented that investigators are quite savvy about light-tissue interactions and potential diagnostic applications. A request for applications (RFA) or program announcement focused on targeted optical contrast agents and necessary hardware, in concert, would generate responses with clearly articulated visions of where the hardware and contrast agent development technologies could go and what medical problems could be solved.

Hardware technology and instrumentation and their associated imaging agents or probes for further research may include:

- Computer-aided imaging
- Nonlinear imaging techniques, e.g. multiphoton
- Surface-enhanced Raman scattering
- Photonics
- Diffuse optical imaging
- Application of optical imaging techniques to clinical problems such as image-guided diagnosis, pathology for diseases such as glioblastoma, traumatic brain injury, and neurological diseases.

PRG members also cautioned against focusing new initiatives on specific research areas rather than supporting basic science and technology development in optics, with the understanding that new technologies should be applicable to the clinic in a reasonable amount of time. PRG members underscored this by referencing GFP and multiphoton microscopy as examples that had been developed years before but are only now broadly

used in biomedical research. Sometimes it is not clear at the time which technologies will have a wide biomedical impact.

The potential for clinical applications of optical imaging

Although optical imaging technologies are appealing, seeing beyond a centimeter in depth remains a challenge. There was some debate in response to Dr. Pettigrew's question about the ability to overcome this limitation. Some PRG members noted promising technological developments, including nonlinear optics; fluorescently labeled probes; use of fiber probes; *in vivo* optic tomography; mesoscopy, including fluorescence and hybrid approaches; and diffuse optical imaging that combines spectroscopic tools with multimodality methods. To provide an example, Dr. Tom Meade discussed new probes that are as bright as Q-dots, without the associated toxicity, and suggested that these probes could be implemented as endoscopic based sensors. Dr. Stephen Lane discussed advances in single-cell microscopy, including the use of photoactivatable fluorescent dyes for super-resolution microscopy and Raman scattering for single cell spectroscopy and label free imaging. Dr. Bruce Tromberg noted the application of TPM to collagen, which has opened a new way for *in vivo* imaging. Applications of optical imaging to view hypoxia and glioblastoma, as well as advances in image-guided therapies, were also discussed.

Other PRG members expressed caution about overselling the promise of optical imaging technology. Dr. John Frangioni noted the drop in resolution for every centimeter of depth within the body, as well as other physical limitations, and suggested that optical imaging would more likely fill niche roles in the clinic. He further suggested that efforts be focused on these niche roles. Dr. Lane agreed that optical imaging would fill a large number of niches and should not be oversold. Other PRG members echoed the view that optical imaging would not replace general techniques such as x-ray or biopsy, but they pointed out that optical imaging could strengthen these techniques. For example, Dr. Tromberg noted that optical imaging could add guidance thereby strengthening the ability to perform biopsies and follow at-risk patients in a noninvasive way.

In response to questions about transmission problems in the biologic milieu, Dr. Tromberg noted the current reliance on endogenous contrast and the richness of this contrast that was revealed with new technologies. Dr. Frangioni noted a class of fluorophores, heptamethine indocyanines, which could successfully detect clinical targets. They agreed that applying optical imaging in the clinic will require partnerships between probe developers and instrument developers. Although understanding of interactions between light and tissue has increased, chemistry and probe design is needed to provide exact answers.

The amount of resolution needed for an optical imaging technique to be useful in the clinic was debated. As a clinician, Dr. Reuben Mezrich argued that optically detecting and characterizing one centimeter size lesion would be useful for screening and diagnosis. Dr. Mezrich further argued that the major hurdle to applying optical imaging in the clinic is not resolution but the need for targeted contrast agents. Dr. Frangioni contended that optical imaging techniques would have to achieve millimeter resolution to

impact medicine. Dr. Tromberg argued that the ability to image across spatial scales, from nanometers to centimeters, is a strength of optical imaging. He added that depth versus resolution could be adjusted based on the type of question needed to be answered.

Dr. Frangioni discussed his work with QDots to illustrate the type of adaptations needed to realize the potential for optical imaging in the clinic. He and his team recognized that QDots might not be good optical probes but had important and interesting properties. They went on to design smaller QDots, about 5 nm, which could be cleared from the body and thus are more likely to be approved by the U.S. Food and Drug Administration (FDA).

Dr. Frangioni and colleagues are now targeting these QDots to tumors, but it is not clear how far the QDot field can go. Likewise, several applications have been developed using nanocrystals that are not based on heavy or semiconductor metals, but clinical translation will be difficult unless these nanocrystals can be cleared from the body. By Dr. Frangioni's standard, nanocrystals should be less than 5 nm in size (or if larger, be able to break down to components less than 5 nm in size) and nontoxic.

Pathology also was discussed as another area where optical imaging could be transformative. PRG members pointed out the need for innovation to develop new dyes and stains, as well as problems with sharing data or slides for multiple opinions. Dr. David Kleinfeld suggested that automated microscopy with supervised learning algorithms could address the need to identify regions of interest on slides. Another PRG member pointed out the synergy between efforts to address pathology needs and those devoted to computer-assisted image analysis for *in vivo* imaging. Dr. Tromberg noted increasing interest among pathologists in optical imaging techniques.

Barriers to translation and clinical applications of optical imaging techniques

PRG members pointed out that the widespread use of OCT in ophthalmology arose after a long and arduous process. FDA approval of OCT occurred in the past 5 years, following approximately a 10 year period to develop the technology and to validate its clinical uses in clinical trials currently. Industry is not motivated to develop optical imaging probes or devices. However, there is momentum to develop agents for therapeutic purposes and less so for diagnostics.

Dr. Frangioni suggested that the academic community must lay the groundwork to translate mature technologies into the clinic rather than relying on industry. Increased institutional support is needed to help investigators move past this roadblock. PRG members pointed out that researchers in optical imaging are highly committed and motivated to move technologies beyond development.

Members suggested the following approaches:

- Develop a program for devices, which is equivalent to NCI's Development of Clinical Imaging Drugs & Enhancers (DCIDE) program. The program would exploit the FDA's Investigational Device Exemption (IDE) mechanism and allow investigators to test the technologies they have developed in the clinic. The program

should include experts at the supporting Institute to assist investigators in navigating the regulatory processes involved in translating technologies to the clinic (i.e., FDA requirements). The FDA also should be involved so that it has an understanding of instruments used, phantoms, calibration, etc. Because of its small size, NIBIB has a unique opportunity to implement such a program.

- Choose one technology or molecule to focus on and push forward to ultimately promote as a success story. Develop standards while translating this technology. Having such a success story, as well as an established set of standards, would increase understanding among the outside community, generate interest, and open opportunities for other technologies. The NCI is forming consortia to choose molecules and platforms to move forward. What has happened in the positron emission tomography community can be used as an example for successes as well as for lessons learned.

As the PRG discussed possible examples, Dr. Frangioni commented that pharmaceutical companies are looking for billion dollar drugs, that small-animal imaging serves as a surrogate, and that for the most part, industry now has what it needs in this area. Other than some recent improvements in free-space optical tomography, he felt the field of small-animal imaging had matured to a point that microCT, microPET, and microSPECT were more or less turn-key.

Dr. Rebecca Richards-Kortum noted that researchers focused on drug-delivery devices had not traditionally turned to optical technology because of cost. She noted, however, that these researchers had easy access to various optical technologies to use with their research, and she pointed out that the drug-delivery device community is substantial. Dr. Tromberg commented that although accessibility has been increased, less is known about end points and what the measurements mean, particularly with optical probes. He cautioned that pharmaceutical companies do not understand the optical researchers' discoveries. The optics community is starting to provide some quantitative end points, but how to interpret these numbers is not yet clear.

Dr. Zhang noted that many processes are biology specific and that imaging solutions should adapt. He agreed that imaging solutions will only work if everyone understands what they see, and he added that general imaging devices would not be appropriate for that type of work. Dr. Zhang also noted opportunities in probe development.

- Choose a major clinical problem with “low-hanging fruit” and issue an RFA to address that problem. NIBIB should add the requirement that any research supported under an RFA should lead to a clinical trial of the new technology. The choice of clinical problem should be the decision of NIBIB, not of study sections. In addition, the choice of clinical problem should be realistic in terms of the kinds of questions optical imaging can answer. Dr. Frangioni suggested that optical imaging technology more likely would fill a niche. Dr. Tromberg mentioned optically guided therapies, such as image-guided surgery for prostate cancer, as one example. Dr. Mezrich listed

breast, skin, colon, airway, and gastrointestinal tract as accessible areas. Brain cancer is another potential problem to which optical imaging could be applied.

- Conduct a formal analysis of barriers to translation and then find a way to overcome them. PRG members agreed that the experiences they had shared were anecdotal. One PRG member noted a clinical science award attempting to identify such barriers.
- Increase the number of P01s awarded, which would provide an opportunity for probe, technology, and clinical applications experts to work together to solve a problem. NIBIB does not have to fund these awards exclusively; rather, the Institute can work with categorical ICs to leverage its portfolio and further research on their disease interests. Connecting to categorical ICs, driving the application of these technologies, could increase the influence of NIBIB.
- Create or support programs that cultivate relationships between clinicians and basic scientists in technology development. Dr. Tromberg noted successful programs where clinical fellows or residents spend 6 months in basic technology research laboratories. The fellows or residents engage fully in the laboratory, attend group meetings, talk with graduate students and postdoctoral candidates, and learn the technology. At the same time, students and postdoctoral candidates learn more about the clinical problems to which their technology might apply.

Balancing translational research and basic research

The PRG agreed that NIBIB should continue to support all steps of translating new technologies to the clinic, and members emphasized that NIBIB has a special role in supporting basic research and technology development. Although translational efforts are important, translation cannot occur without new development. Thus, basic research is vital to maintain a rich and continuous pipeline, and it should not be ignored. That being said, however, NIBIB cannot lose sight of the overall NIH mission to improve health care. Thus, NIBIB recognizes the importance of basic research and aims to support it, but also aims to identify the greatest opportunities for translation.

There was some debate on how to achieve such a balance. On the one hand, Dr. Frangioni observed that it is incumbent on study sections to support grants that had clinical potential and that would someday benefit the taxpayers funding the work. He questioned whether NIBIB should ensure that the projects it supports improve human health in the short-term rather than long-term. Dr. Kleinfeld, on the other hand, noted the difficulty in knowing a priori which basic research projects would ultimately affect human health. He cited two examples, green fluorescent protein (GFP), and TPM, which started out as basic science innovations. GFP was developed as a way to mark cells and as a platform for functional probes, and TPM was developed to address problems of photobleaching, but now, more than a decade later, both innovations have had a large impact. Dr. Kleinfeld concluded by citing the danger of focusing only on short-term clinical potential.

PRG members noted that when moving a technology into the clinical domain, researchers and Institutes should have a strong appreciation for the clinical problem and its underlying biological components. They asked at what stage NIBIB passes a developing biomedical technology to a disease-focused Institute. Dr. Pettigrew indicated that the determination is made on a case-by-case basis but that NIBIB viewed technology development as its domain and the application of that technology to clinical problems as the domain of the appropriate categorical IC. To illustrate this point, Dr. Heetderks noted a collaboration between NIBIB and the National Institute of Child Health and Human Development (NICHD) on prosthesis and medical rehabilitation, where support gradually transfers from NIBIB to NICHD as the focus moves from technology development and feasibility to clinical trials and application. Dr. Pettigrew also noted a discussion with an NHLBI grantee who proposed the development of a means to measure blood pressure without the traditional cuff. Again, the development of such a technology would fall in the domain of NIBIB, whereas the clinical application would be the domain of NHLBI.

NIBIB enjoys strong relationships with most categorical ICs and will continue to collaborate with them on grant applications worthy of funding. For example, the National Institute on Aging and NIBIB are collaborating on the imaging component of a project focused on the natural history of Alzheimer's disease, and NIBIB and the National Institute of Arthritis and Musculoskeletal and Skin Diseases are collaborating on an osteoarthritis study. Historically, categorical ICs have approached NIBIB about collaboration. NIBIB has not typically approached other ICs about a maturing technology.

PRG members noted that institutions constantly focused on novel techniques but did not focus also on putting forward likely candidates for translation. They agreed on the importance of supporting efforts to identify strategies to address intractable problems rather than have investigators just “crank out new molecules” in response to RFAs. PRG members also noted that support of such efforts should not occur at the expense of support of basic science and technology development. They suggested an intermediate step between discovery and translation—consensus forming—in which teams are funded to develop a consensus approach. The Network for Translational Research in Optical Imaging Program, in which Dr. Tromberg participates, is an example. Dr. Seto also noted an NIH-wide initiative, led by the NCI, to foster the Small Business Innovation Research community puts forward a fraction of technologies ripe for translation. NIBIB has formed a partnership with this initiative to implement development centers for this purpose.

Dr. Kleinfeld commented on NIBIB's goal of an intramural program with interdisciplinary emphases. He discussed two meetings at Cold Spring Harbor where many groups were committed to neuroscience research but included expertise in chemistry, biology, and optics. He pointed out that because team members had training in specific disciplines, they were able to make strong contributions to the team, and the team thus exerted a stronger impact than teams focused on one discipline alone. He cautioned against training any one person to be “interdisciplinary.” Instead, he suggested that interdisciplinary research be defined by teams in which each member has his or her own area of expertise.

Emphasis on innovation

For the past 2 years, NIBIB has played the lead role in a NIH Roadmap initiative that charges investigators with developing novel probes, with the understanding that many of these attempts may fail and not proceed to clinical uses. The initiative also required that investigators would extend beyond cells, tissues, and animal models and translated to clinical applications. PRG members cautioned the NIBIB and NIH against initiatives that inhibit collaboration and creativity. Several members supported continued use of the R01 mechanism because of its flexibility. Dr. Kleinfeld suggested an RFA or program announcement to encourage exploration of good ideas that are not hypothesis driven. These types of applications are typically unsuccessful in traditional study sections.

The PRG also discussed the challenge of forming and educating study sections to review high-risk/high-impact research proposals. Dr. Meade emphasized that study sections should have a balance of representatives from imaging and chemistry. The PRG and NIBIB staff noted some challenges to creating this balance, however. Development of such study sections occurs slowly. Although NIBIB has a collegial relationship with the Center for Scientific Review and makes recommendations for study section participants, the Scientific Review Administrator makes the final decisions. Moreover, science has become so interdisciplinary that study sections might not be appropriate for an entire roster of applications as they may have been in the past.

The PRG pointed out that encouragement of new investigators is especially important because newer investigators tend to be most innovative. However, the current funding climate places a pressure on institutions to write as many grant applications as possible, which in turn drives the formation of collaborative groups. This climate thus places smaller laboratories and new investigators at a disadvantage. NIBIB budget accounts for about 1% of the NIH budget but 2% of the total number of NIH-supported new investigators. In the past year, just under one-third of NIBIB awards went to new investigators, compared with more than 20 percent for the rest of NIH. Although NIBIB has a large number of new investigators, more are needed. Drs. Pettigrew and Seto discussed NIH initiatives to encourage new investigators, such as pathway to independence awards, pioneer awards, innovator awards, and R01 bridge awards for new investigators.

Training is also critical to promote innovation. Often the imaging and pharmaceutical fields use the same words to describe different phenomena. Although NIBIB has a training grant program that focuses on core, interdisciplinary, and resident training, PRG members perceived that training was underfunded. The PRG agreed that NIBIB is in a unique position to train biomedical engineers who can move into the pharmaceutical industry and facilitate the translation of developed technologies into practical tools. The Institute could implement a formal program to facilitate the retraining of physicists, chemists, and engineers to address biomedical problems. More training grants also could help biology departments to train people from nontraditional areas. PRG members pointed out that the number of Medical Scientist Training programs for M.D./Ph.D. students has been drastically reduced. This number should be expanded.

The value of NIBIB-supported research in optical imaging

The PRG and NIBIB leadership agreed on the need to clearly articulate the value of NIBIB-supported research. NIBIB grantees have been challenged by problems with the translational pipeline, including legal and intellectual property issues. Institutional support for obtaining IDEs and eINDs from the FDA would go a long way in showing Congress how basic science ultimately results in improved human health. PRG members suggested a 5-year goal: To show evidence that principal investigators have been able to translate their discoveries to the clinic because of NIBIB support. The PRG also suggested the establishment of a NIBIB office to work with the FDA to establish a clear pathway for translation of optical technologies. In addition, the optical imaging community has a responsibility to realistically and honestly assess which technologies ripe for translation are most likely to have an impact in the clinic. Several PRG members suggested that optical imaging technologies would most likely benefit underserved niche applications, such as neuroimaging or gastrointestinal imaging.

Dr. Tromberg pointed out that many device trials—including studies of optical imaging techniques—might be missed by clinicaltrials.gov. For example, his institution has 23 studies testing techniques in the clinic, but these trials are not included in the database. Dr. Seto invited PRG members to submit information about these trials so that NIBIB and the National Library of Medicine, which administers the clinicaltrials.gov site, can make sure they are included.

PRG members agreed that NIBIB had done well in forming a mission statement and articulating several goals. They also agreed that NIBIB, an Institute supporting discovery and basic research in technology development, has successfully juggled various enterprises. Yet, the Institute must help the rest of the biomedical research community to understand how advances in imaging form a critical component of the community's economy. The pace of translation might be frustrating, but these advances have a large impact by facilitating further discovery.

Summary

NIBIB is committed to improving human health by leading the support of basic research in technology development and accelerating the application of biomedical technologies. Continued NIBIB support for basic research will allow room for serendipity because some technologies might have far more impact than originally envisioned.

Yet, NIBIB also must support all steps of the discovery-translation pipeline (a.k.a. critical path initiative), including the translation of mature technologies into the clinic. The best approach to translation is the formation of partnerships with categorical ICs to achieve an understanding of both the clinical problem and imaging constraints, and to ensure that risks and responsibilities are shared. In promoting these types of relationships, NIBIB could leverage itself as a resource and serve as a model for all of NIH. In addition, NIBIB should consider adding a funding step—consensus-forming—to address the interface between discovery and translation. This additional step will support efforts to identify technologies ready for translation.

The PRG did not see egregious gaps in the Optical Imaging Program research portfolio. Instead, they discussed opportunities for moving technologies forward and achieving success stories. Clinical success stories cannot be ignored because they help illustrate how the Institute can support the development of emerging technologies into tools to improve health care. NIBIB should choose a major clinical problem with low-hanging fruit in an accessible organ, such as the skin, colon, breast, or airway, and then support research leading to a clinical trial of a new technology. It should be emphasized that the choice of clinical problem should be the decision of the Institute, not of individual study sections, and it should be realistic in terms of which problems can be addressed by optical technologies.

Attachment 1

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